

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: RICHARD R. MYBECK
8010 EAST MORGAN TRAIL
SUITE 10
SCOTTSDALE, AZ 85258

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	22 JUN 2000
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Applicant's or agent's file reference 5367-PCT	IMPORTANT NOTIFICATION
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International application No. PCT/US99/00475	International filing date (day/month/year) 09 JANUARY 1999	Priority Date (day/month/year) 09 JANUARY 1998
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Applicant ARIZONA BOARD OF REGENTS
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1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

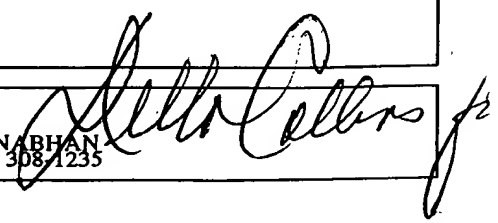
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Form PCT/IB/301 (05-1990)★ Washington, D.C. 20231	Authorized officer SREENI PADMANABHAN (703) 308-1235
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5367-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/00475	International filing date (<i>day/month/year</i>) 09 JANUARY 1999	Priority date (<i>day/month/year</i>) 09 JANUARY 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ARIZONA BOARD OF REGENTS		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>4</u> sheets.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step or industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application
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Date of submission of the demand 09 AUGUST 1999	Date of completion of this report 24 APRIL 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Form PCT/IPEA/409 (205-3392) (July 1998)★ Washington, D.C. 20531	Authorized officer SREENI PADMANABHAN

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
- pages 1-29, as originally filed
- pages NONE, filed with the demand
- pages NONE, filed with the letter of _____

- ☒ the claims:
- pages 1-5, as originally filed
- pages NONE, as amended (together with any statement) under Article 19
- pages NONE, filed with the demand
- pages NONE, filed with the letter of _____

- ☒ the drawings:
- pages 1-5, as originally filed
- pages NONE, filed with the demand
- pages NONE, filed with the letter of _____

- ☒ the sequence listing part of the description:
- pages NONE, as originally filed
- pages NONE, filed with the demand
- pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

Form PCT/US 99-1 (Rev. 10/99) For PCT applications (Article 14) furnished to the receiving Office in response to an invitation under Article 14 are referred to

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>NONE</u>	YES
	Claims	<u>1-5</u>	NO
Inventive Step (IS)	Claims	<u>1-2 and 4-5</u>	YES
	Claims	<u>3</u>	NO
Industrial Applicability (IA)	Claims	<u>1-5</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-5 lack novelty under PCT Article 33(2) as being anticipated by Cushman et al. (US patent No. 5,430,062).

Cushman discloses phenstatin compounds and derivatives claimed in the instant invention (see for example compound 27, columns 19-20). Cushman also teaches the use of these compounds as anti-cancer drugs.

Claim 3 lacks an inventive step under PCT Article 33(3) as being obvious over Pettit et al. (US patent No. 4,996,237).

Pettit teaches the use of similar compounds, combrestatins, for the inhibition of cancer cell growth and tubulin polymerization. Such a teaching renders the applicants teaching of similar phenstatin prodrugs an obvious extrapolation of Pettit's teachings.

Claims 1-2 and 4-5 meet the criteria set under PCT Article 33(3).

Claims 1-5 meet the criteria set out under PCT Article 33(4).

----- NEW CITATIONS -----

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

Supplemental B x

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A61K 31/09, 31/075, 31/66; C07C 43/215, 217/80 and US Cl.: 514/646, 720, 130, 721; 568/331, 332, 631, 646

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:

NONE

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 September 1999 (22.09.99)	
International application No. PCT/US99/00475	Applicant's or agent's file reference 5367-PCT
International filing date (day/month/year) 09 January 1999 (09.01.99)	Priority date (day/month/year) 09 January 1998 (09.01.98)
Applicant PETTIT, George, R. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
09 August 1999 (09.08.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. Forax
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 16 MAR 2001

WIPO

PCT

Applicant's or agent's file reference 5367-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/00475	International filing date (day/month/year) 09 JANUARY 1999	Priority date (day/month/year) 09 JANUARY 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ARIZONA BOARD OF REGENTS		

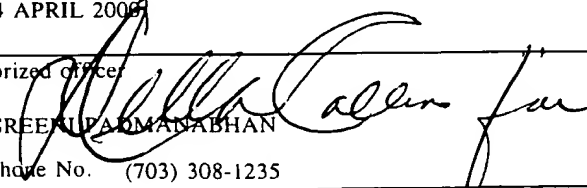
- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 4 sheets.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

**CORRECTED
VERSION**

Date of submission of the demand 09 AUGUST 1999	Date of completion of this report 24 APRIL 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  SREENI PADMANABHAN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

I. Basis of the report**1. With regard to the elements of the international application:***☐ the international application as originally filed☒ the description:

pages _____ (See Attached) _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages _____ (See Attached) _____, as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages _____ (See Attached) _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:

pages _____ (See Attached) _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages _____ NONE _____☒ the claims, Nos. _____ 1 AND 2 _____☒ the drawings, sheets/fig. _____ NONE _____**5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

V. Required statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)

Claims NONE YESClaims 1-3 NO

Inventive Step (IS)

Claims NONE YESClaims 1-3 NO

Industrial Applicability (IA)

Claims 1-3 YESClaims NONE NO**2. citations and explanations (Rule 70.7)**

Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by Cushman et al. (US patent No. 5,430,062).

Cushman discloses phenstatin compounds and derivatives claimed in the instant invention (see for example compound 27, columns 19-20). Cushman also teaches the use of these compounds as anti-cancer drugs.

Claims 1-3 lack an inventive step under PCT Article 33(3) as being obvious over Pettit et al. (US patent No. 4,996,237).

Pettit teaches the use of similar compounds, combrestatins, for the inhibition of cancer cell growth and tubulin polymerization. Such a teaching renders the applicants' teaching of similar phenstatin prodrugs an obvious extrapolation of Pettit's teachings.

----- NEW CITATIONS -----

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A61K 31/09, 31/075, 31/66; C07C 43/215, 217/80 and US Cl.: 514/646, 720, 130, 721; 568/331, 332, 631, 646

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-29, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) NONE, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Page 30 filed with the letter of 01 February 2000.

This report has been drawn on the basis of the drawings,
page(s) 2-5, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
Page 1 filed with the letter of 02 February 2000.

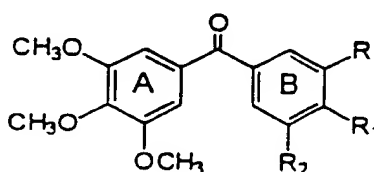
This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

Claims

1. The method of inhibiting cancer cell growth and tubulin polymerization in an environment inflicted therewith comprising: introducing into said environment a pharmaceutically acceptable carrier and a small but effective amount of phenstatin prodrug.

2. Phenstatin prodrugs and derivatives thereof having the structure:

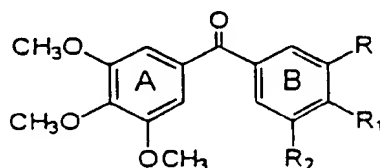
10



wherein when $R=H$ and $R_1 = OCH_3$, R_2 is OPO_3NA_2 , $OCOCH_3$, or OCH_3 and when $R=R_2$, R_2 is OCH_3 , CH_3 , Cl or F and R_1 is H and when $R_1=R_2$, R_2 is OCH_3 or OCH_2O and R is H .

3. The method of inhibiting human cancer cell growth in a host inflicted therewith comprising administering to said host in pharmaceutically acceptable carrier a small but effective amount of a compound selected from the group consisting of phenstatin, phenstatin prodrug and the derivatives thereof having the structure.

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wherein when $R=H$ and $R_1 = OCH_3$, R_2 is OPO_3NA_2 , $OCOCH_3$, or OCH_3 and when $R=R_2$, R_2 is OCH_3 , CH_3 , Cl or F and R_1 is H and when $R_1=R_2$, R_2 is OCH_3 or OCH_2O and R is H .

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/00475

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/09, 31/075, 31/66; C07C 43/215, 217/80

US CL :514/646, 720, 130, 721; 568/331, 332, 631, 646

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/646, 720, 130, 721; 568/331, 332, 631, 646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,430,062 A (CUSHMAN et al) 04 July 1995, Whole Document.	1-5
Y	US 4,996,237 A (PETTIT et al) 26 February 1991, Whole Document.	1-3
A	US 5,561,122 A (PETTIT) 01 October 1996, Whole Document.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 MARCH 1999

Date of mailing of the international search report

25 MAR 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SREENI PADMANABHAN for

Telephone No. (703) 308-1235

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/09, 31/075, 31/66, C07C 43/215, 217/80	A1	(11) International Publication Number: WO 99/34788 (43) International Publication Date: 15 July 1999 (15.07.99)
(21) International Application Number: PCT/US99/00475 (22) International Filing Date: 9 January 1999 (09.01.99) (30) Priority Data: 60/070,878 9 January 1998 (09.01.98) US (71) Applicant (for all designated States except US): ARIZONA BOARD OF REGENTS, a body corporate, acting on behalf of ARIZONA STATE UNIVERSITY [US/US]; Tempe, AZ 85287 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): <u>PETTIT</u> , George, R. [US/US]; 6232 Bret Hills Drive, Paradise Valley, AZ 85253 (US). <u>TOKI</u> , Brian [US/US]; Apartment 1090, 1500 East Broadway Road, Tempe, AZ 85282 (US). (74) Agent: MYBECK, Richard, R.; Suite 10, 8010 East Morgan Trail, Scottsdale, AZ 85258 (US).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: SYNTHESIS OF PHENSTATIN AND PRODRUGS THEREOF (57) Abstract A newly discovered antineoplastic compound denominated "phenstatin" is herein described as are synthetic methods for producing phenstatin and the active prodrug thereof. Phenstatin was converted to the sodium phosphate prodrug (3d) by a dibenzylphosphite phosphorylation and subsequent hydrogenolysis sequence 3b→3c→3d. Phenstatin (3b) was found to be a potent inhibitor of tubulin polymerization and the binding of colchicine to tubulin comparable to combretastatin A-4 (1b).		